

clude initial tissue loading, adequate retention with sustained release kinetics, and cellular uptake. To evaluate one approach to LD of ODN, we injected 2 ml of a lipid-ODN solution ([18-mer ODN] = 0.57 mg/ml) into the sites of balloon overstretch angioplasty in coronary arteries of normal pigs, using a porous balloon catheter (USCI Inc.) at 4 ATMs for 20 sec. ODN were labelled with ^3H (3.75 $\mu\text{Ci/ml}$) or rhodamine. Samples were harvested at 30 min, and 2 and 24 hr and processed for scintillation counting or fluorescence microscopy.

Time	Concentration of ODN, $\mu\text{g/g}$ tissue		
	uninjured coronary	injured, no ODN	injured + ODN
30 min	0.15	1.79	30.46
2 hr	0.07	0.03	10.06
24 hr	0.03	0.00	0.62

By scintillation counting the percentage delivery of the injectate to the injured coronary artery was 0.31% at 30 min, which decreased to 0.13% at 2 hr and 0.01% by 24 hr. Radioactivity of various organs was at background level except heart, lung, liver, and kidney. Fluorescence microscopy demonstrated localization of ODN at 30 min and 2 hr primarily in the adventitia near the medial rupture; label was scarcely detectable at 24 hr. Only rare instances of intracellular localization were observed.

Conclusion: LD of ODN by porous balloon results in low acute transfer and rapid tissue loss, suggesting poor potential for biological effects. Alternative strategies such as iontophoresis and electroporation are under investigation.

938-43 Reduced Thrombogenicity of Polished and Unpolished Nitinol vs. Stainless Steel Slotted-Tube Stents in a Pig Coronary Artery Model

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The thrombogenicity of slotted-tube stents made of nitinol (polished and unpolished) or stainless steel (Palmaz-Schatz) was assessed in a pig coronary artery model. Six nitinol stents were polished mechanically. Six polished nitinol, six unpolished nitinol and five stainless steel stents (15 mm long) were deployed in the mid portion of LAD of 17 pigs with a 3.0 mm balloon, inflated twice at 6 atm for 20 seconds. Oral aspirin and diltiazem as well as intravenous heparin were administered prior to implantation of the stent. All pigs were euthanized after 6 days. Immediately after sacrifice, the heart was removed and the stented segment of LAD was excised and cut open. The amount of thrombus on each stent was assessed by a semiquantitative grading scale (I: no lumen encroachment; II: lumen encroachment; III: subocclusive thrombus and IV: occlusive thrombus) and by the weight of the dry thrombus. Histologic examination of the stented arterial segments was performed after H&E staining to evaluate vascular injury. **Results:**

Parameter	Stainless Steel	Unpolished Nitinol	Polished Nitinol	ANOVA p-value
n	5	6	6	
Thrombus Weight (mg)	9.2 \pm 0.3	1.8 \pm 1.3	0.6 \pm 0.07	<0.00001
Thrombus Grade (I to IV)	II = 5	I = 5, II = 1	I = 6	<0.0001

Histologic examination of the stented arterial segments showed that all 5 animals in the group with stainless steel stents had a deeper stent strut strut penetration with diffuse, transmural medial necrosis and thinning, compared to none in the groups with nitinol stents (5/5 vs. 0/12; $p = 0.0002$).

Conclusions: Both polished and unpolished nitinol stents developed significantly less thrombus in comparison to stainless steel stents of similar design as measured by thrombus weight and thrombus grade in the pig coronary artery model. Polished nitinol stents were found to be even less thrombogenic than unpolished nitinol stents. More severe vascular injury may contribute to the higher thrombogenicity of stainless steel stents in this model.

938-44 Fibrin Coated Stents as a Depot to Deliver RGD Peptide Inhibit Vascular Reaction in Atherosclerotic Rabbit Model

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Despite therapeutic success of intracoronary stent implantation, stenting of small vessels remains a problem. Our previous studies of coating metallic stents with biocompatible compounds such as fibrin demonstrated reduced thrombogenicity and the potential for drug delivery. RGD peptide inhibits the interaction of fibrinogen with platelet membranes. We determined the impact of fibrin coated stents loaded with RGD peptide upon restenosis in an atherosclerotic rabbit model. Coated and uncoated novel radially expandable "PEAK" metallic stents were implanted in contralateral areas of 10 rabbit iliac arteries previously denuded of endothelium and placed on a diet supplemented with 2% cholesterol for 3 weeks. QCA and morphometric analysis

data obtained 4 weeks following stent implantation revealed that 1) late loss was significantly less in coated group compared with uncoated group (0.12 ± 0.01 vs 0.45 ± 0.05 , $p < 0.01$), and 2) the extent of myointimal hyperplasia as defined by histologic analysis was significantly lower in coated than that of the uncoated stent with minimal smooth muscle proliferation using PCNA or inflammatory cell infiltration. Planimetric analysis of vessel cross sectional area also revealed less hyperplasia in coated versus uncoated stents (3.5 ± 0.9 vs 16.4 ± 2.8 , $p < 0.01$). We conclude that RGD loaded fibrin coating inhibits vascular reaction following stent implantation.

939 Restenosis: Basic Insight

Tuesday, March 26, 1996, 9:00 a.m.-11:00 a.m.
Orange County Convention Center, Hall E
Presentation Hour: 10:00 a.m.-11:00 a.m.

939-45 Remodeling and Plaque Formation in Restenosis: Effects of Colchicine and Enoxaparin in the Atherosclerotic Rabbit

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Colchicine (Colc) and enoxaparin (Enox) reduce restenosis after angioplasty (A) in the hypercholesterolemic rabbit model. This study examines the contributions of arterial remodeling (differences in external elastic lamina (EEL) area) and plaque formation (differences in intima + media (I + M) area), to this reduction. Rabbits underwent iliac artery de-endothelialization and were fed a 1.5% cholesterol diet for 6 weeks, at which time A was performed in arteries with $\geq 50\%$ stenosis. Treatment groups included Colc (0.2 mg/kg/d, $n = 12$), Enox (10 mg/kg/d, $n = 8$) and A alone ($n = 11$). There were no differences in pre-A, post A, or reference minimal lumen diameter (MLD). All groups underwent angiography 4 weeks post A and quantitative histology of the most stenotic section was performed.

	A Alone	Enoxaparin	Colchicine
Angio MLD (mm)	0.6 \pm 0.1	1.2 \pm 0.1 [†]	1.1 \pm 0.6*
EEL area (mm ²)	3.94 \pm 0.79	2.88 \pm 1.33*	5.24 \pm 1.89*
I + M area (mm ²)	3.37 \pm 0.68	2.25 \pm 1.06 [†]	4.41 \pm 1.88

Mean \pm SD, * $p < 0.04$, [†] $p < 0.01$ vs. A Alone

Compared with A alone, Colc arteries had a greater I + M area, but because of a greatly increased EEL area, the lumen was still significantly larger. In contrast, Enox treated arteries showed less remodeling, as the EEL area was smaller. However, because of a much smaller I + M area, the lumen remained significantly larger. Thus, Colc reduces restenosis through enhancing remodeling while Enox reduces restenosis via a reduction in plaque formation. This study demonstrates a differential effect of drugs on two principle processes of restenosis: plaque formation and remodeling.

939-46 The Immediate Early Gene Products of Human Cytomegalovirus Increase Vascular Smooth Muscle Cell Migration

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Increasing evidence suggests human cytomegalovirus (HCMV) infection contributes to the development of atherosclerosis and of restenosis; if it does, then the cellular effects of its immediate early (IE) gene products likely play a central role. Since smooth muscle cell (SMC) migration from media to intima is a crucial event of atherogenesis and restenosis, we determined whether HCMV infection increases this process. HCMV rapidly replicates and produces cytopathic effect (CPE) soon after infecting human SMCs; however, we found that only IE gene products are expressed when HCMV infects rat SMCs (RSMCs) and CPE does not occur. We therefore infected RSMCs with high HCMV titers such that 30-40% of cells expressed IE72 and IE84. Since peak expression occurred 3 days post infection (PI), we compared migration rate of infected and noninfected RSMCs 3 days PI using a modified micro-Bayden chamber: cells are placed in 0.5% FBS in the upper chamber, and in PDGF or 10% FBS in the lower. As previously shown, PDGF (0.1-20 ng/ml) increased migration of SMCs in a concentration-related manner. HCMV significantly augmented the response to PDGF (116 ± 51 cells per high power field migrated vs 64 ± 37 ; $p < 0.01$). However, HCMV did not significantly alter the response to 10% FBS. **Conclusion:** HCMV infection of SMCs, and specifically HCMV's IE gene products, increase the SMC migration response to PDGF. This finding adds an additional mechanism by which CMV may contribute to the development of neointimal lesions, and thereby provides further evidence suggesting that CMV plays a crucial role in the development of restenosis and of atherosclerosis.